One evidence base; three stories: do opioids relieve chronic breathlessness?

ABSTRACT

The efficacy of low-dose systemic opioids for chronic breathlessness was questioned by the recent Cochrane review by Barnes *et al*. We examined the reasons for this conflicting finding and re-evaluated the efficacy of systemic opioids. Compared with previous meta-analyses, Barnes *et al* reported a smaller effect and lower precision, but did not account for matched data of crossover trials (11/12 included trials) and added a risk-of-bias criterion (sample size). When re-analysed to account for crossover data, opioids decreased breathlessness (standardised mean differences −0.32; −0.18 to −0.47; I^2=44.8%) representing a clinically meaningful reduction of 0.8 points (0–10 numerical rating scale), consistent across meta-analyses.

INTRODUCTION

Chronic breathlessness[1] is common across a range of advanced diseases and associated with major adverse health outcomes.[2] The candidate treatment with best evidence to date is regular, low-dose, non-nebulised (systemic) morphine.[2] The efficacy of low-dose systemic opioids was supported by a Cochrane review by Jennings *et al*,[3 4] an adequately powered crossover trial in 2003,[5] and the meta-analysis in people with severe COPD by Ekström *et al*.[6]

A new Cochrane meta-analysis by Barnes *et al*,[7] drawing from a similar evidence base, reported a smaller benefit of opioids than the other reviews, and wider 95% CIs which nearly crossed zero. The risk of bias was rated as 'high' for all studies; previous ratings were mainly 'unclear' or 'low'.[3 4 6] Barnes *et al*[7] rated the quality of evidence for opioids for breathlessness as 'very low'.

We aimed to determine the reasons for the different conclusions and to

Table 1 Characteristics of meta-analyses of systemic opioids for breathlessness

Characteristic of meta-analysis	Jennings *et al*[3]	Ekström *et al*[6]	Barnes *et al*[7]
Design of included studies (n)	Double-blind RCTs	Double-blind RCTs	Double-blind RCTs
N studies	9 (all crossover trials)	8 (all crossover trials)	12 (1 parallel and 11 crossover trials)
N trial participants	102	118	198
Population (n trial participants)	COPD (n=80) Chronic heart failure (n=12) Cancer (n=10)	COPD (n=113) Other (n=5)	COPD (n=107) CHF (n=47) Cancer (n=41) Other (n=3)
Intervention	Oral or parenteral opioid	Oral or parenteral opioid	Oral or parenteral opioid
Comparison	Placebo	Placebo	Placebo or any other pharmacological or non-pharmacological interventions that were directly compared with the opioid treatment (only two trials used non-placebo comparator)
Duration of treatment (n studies)	Single or few doses (N=5); longer treatment of 1–6 weeks (n=4)	Single dose or 1 day (n=3); 4 days to 6 weeks (n=5)	Single dose or 1–2 days (n=7); 4 days to 6 weeks (n=5)
Statistical method for pooling	Random effects model. Change on different scales compared as SMDs	Random effects model. Change on different scales compared as SMDs	Fixed effect models. Changes compared as MD when on the same scale and SMD when on separate scales, and separately for change from baseline and postscores. Random effects model was used in a sensitivity analysis
Accounted for crossover designs	Yes	Yes	No (analysed data as from parallel trials)
Findings for whole study population			
Pooled effect of opioids (95% CI; I^2; n trial participants)*	SMD −0.40 (−0.63 to −0.17; I^2=42.3% ; n=102)	SMD −0.34 (−0.58 to −0.10; I^2=0%; n=118)	Oral opioid, change from baseline: SMD 0.07 (−0.30 to 0.44; I^2=65%; n=116) Oral opioid, postscores: SMD −0.27 (−0.56 to 0.02; I^2=0%; n=190) Subcutaneous opioid, change from baseline: MD 0.20 (−2.50 to 2.90; n=20)
Stated quality of evidence	Not stated	Moderate (GRADE)	Not stated for systemic opioids For opioids overall: very low for change from baseline and low for postscores (GRADE)†
Findings in COPD participants			
Pooled effect of opioids (95% CI; I^2; n trial participants)*	SMD −0.26 (−0.44 to 0.08; I^2=23.6%; n=80)†	SMD −0.34 (−0.58 to −0.10; I^2=0%; n=118)	Change from baseline: SMD −0.49 (−1.08 to 0.10; I^2=0%; n=46)† Postscores: SMD −0.21 (−0.45 to 0.04; I^2=0%; n=262)†
Stated quality of evidence (criteria)	Not stated	Moderate (GRADE)	Not stated
Risk of bias assessment	Using Jadad score of methods of randomisation and blinded. Most items were rated as unclear	Using the Cochrane risk of bias tool. Ratings were low or unclear for all items; no item was rated as high	Using the Cochrane risk of bias tool as well as an additional item based on study size: ≥200 (low risk), 50–199 (unclear risk) and <50 (high risk) participants in each treatment arm. All items in the Cochrane risk of bias tool were rated as low or unclear except three items rated as high: performance bias (n=1), detection bias (n=1) and other bias (n=1).† Risk of study size bias was rated as high risk for all studies

Characteristics are for trials included in each published meta-analysis.[3 6 7]
*Negative estimate indicates reduction in breathlessness by opioids compared with placebo.
†Included both trials of systemic and nebulised opioids which were not reported separately.
CHF, congestive heart failure; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; I^2, proportion of the total variance in effect estimates that are between studies; MD, mean difference; RCT, randomised controlled trial; SMD, standardised mean difference.

re-evaluate the efficacy of systemic opioids for chronic breathlessness.

METHODS

Data were extracted from the published meta-analyses by Jennings *et al*,[3 4] Ekström *et al*[6] and Barnes *et al*[7] (by ME), and cross-validated (DCC and MJJ) regarding study populations, designs, interventions and methods, for the whole study population and in participants with COPD, respectively.

Breathlessness measures were analysed as standardised mean differences (SMD).[8] For crossover trials, the SE was estimated using the crossover information, directly from the published report or calculated from significance test statistics as recommended.[8] The effect of opioids compared with placebo was analysed using a random effects model. A detailed description of the statistical methods is given in the online supplementary file (appendix 1).

RESULTS

Included studies

All included studies were double-blind, placebo-controlled randomised trials; 13/14 studies were crossover designs (table 1). Jennings *et al* and Barnes *et al* included patients with any advanced, life-limiting disease, whereas Ekström *et al* restricted the analysis to patients with COPD. Research questions, interventions, comparisons and treatment durations were similar between the three meta-analyses (table 1).

The study populations overlapped significantly with over half of the studies by Barnes *et al* also included in studies by Jennings *et al* and Ekström *et al* (see online supplementary table S1). For two studies omitted by Barnes *et al*, the reasons for exclusion were not stated.

Efficacy

In contrast to the other meta-analyses, Barnes *et al* used a fixed effects model which does not account for variations in the true effect between studies, and analysed all data as if from parallel trials and did not account for matched crossover data (11/12; 92% of included studies).

Opioids were associated with a decrease in breathlessness in both studies by Jennings *et al* and Ekström *et al* (table 1). In the primary analysis of Ekström *et al*, systemic opioids improved breathlessness in COPD outpatients measured at *steady state* (5 studies, 91 participants), SMD −0.33 (95% CI −0.52 to −0.14).

Barnes *et al* split the analysis by route of administration and type of outcome measure (table 1). Point estimates of efficacy ranged from SMD −0.27 (oral opioid, post-treatment scores) to mean difference 0.20 (subcutaneous opioid, change scores). Precision was markedly lower across all analyses. The estimate for COPD in the study by Barnes *et al* included all types of both systemic and nebulised opioids. Estimates for systemic opioids or efficacy at steady state were not reported.

When Barnes *et al* was re-analysed using a random effects model accounting for crossover data (figure 1), opioids decreased breathlessness, SMD −0.32 (95% CI −0.47 to −0.18; p<0.001; I^2=44.8%) compared with placebo, consistent with the studies by Jennings *et al* and Ekström *et al*. Using the SD from a large study,[5] this effect size corresponds to a reduction of 0.8 points on a 0–10 numerical rating scale. The finding was consistent when excluding the three studies for which the SEs were imputed.

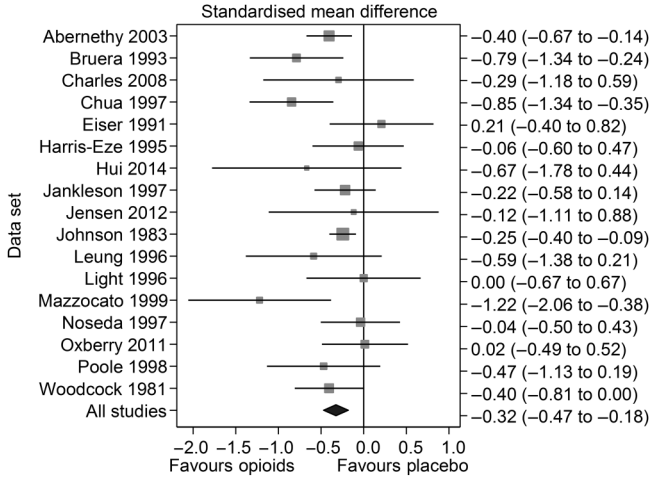

Figure 1 The meta-analysis of Barnes *et al*[7] re-analysed using random effects model and accounting for matched data of crossover trials. In the pooled analysis compared with placebo, systemic opioids reduced breathlessness by a mean 0.32 (95% CI 0.18 to 0.47; p<0.001) SDs.

Risk of bias and quality of evidence

Conclusions regarding risk of bias were similar between the studies by Jennings *et al* and Ekström *et al*, with unclear or low risk of bias for most items (table 1). In contrast, Barnes *et al* categorised all studies as having high risk of bias due to low sample size defined as <50 participants in each treatment arm. This criterion had no stated rationale and resulted in the quality of evidence for systemic opioids being downgraded from moderate (Ekström *et al*) to low or very low in the study by Barnes *et al* (table 1).

DISCUSSION

The conflicting findings regarding the efficacy of opioids for chronic breathlessness in the recent Cochrane review are likely due to their use of inappropriate methodology. When re-analysed to account for crossover data, opioids were associated with a statistically and clinically significant reduction in breathlessness,[9] consistent across meta-analyses.[3 4 6]

Analysing crossover studies as parallel studies can result in selection bias, with spuriously too high or too low effect estimates, as well as reduced precision.[10] Recommended methods to account for crossover data are available[10] and were used by Jennings *et al*4 and Ekström *et al*.[3 6] In addition, study selection should align to predefined eligibility criteria with reasons for exclusion stated to minimise selection bias.

While any judgement of risk of bias is subjective, the bias criterion related to study size introduced by Barnes *et al*, which resulted in all studies being rates as high risk of bias, is questionable. It is the *power* of the study which could lead to bias, and not the sample size per se, which is based on the power calculation. Adequate power can be provided by trials with total sample sizes below 50,[5] especially in crossover trials where the participants act as their own control thus increasing power.

We suggest that the analysis by Barnes *et al* and the relevant guidelines for analysis and review of the Cochrane Collaboration are updated to accommodate these issues.

CONCLUSION

Moderate level evidence to date supports that regular, low-dose morphine is the first-line pharmacological treatment for the relief of chronic breathlessness in severe illness.

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Competing interests DCC has received intellectual property payments and advisory board payments. MJJ has been a clinical consultant for Mayne Pharma. Authors of this paper have longstanding interest in the research of breathlessness and have published several opioid-related trials and meta-analyses (including ME and DCC[6]). MJJ was an external clinical academic (not statistical) peer reviewer for the original Barnes *et al* protocol submitted to Cochrane.

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